PDA Journal of Pharmaceutical Science and Technology

1999

November/December

Volume 53

Number 6

PDA
An International Association For Pharmaceutical Science And Technology

PDA Journal of Pharmaceutical Science and Technology

PDA Journal of Pharmaceutical Science & Technology (ISSN 1079-7440) is published bimonthly by the PDA, Inc., 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

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Periodicals postage paid at Bethesda, Maryland and additional mailing offices. Postmaster: Send address changes to the *PDA Journal of Pharmaceutical Science & Technology,* 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

Printed in the U.S.A.

Formerly the
"Journal of Parenteral Science and Technology"

ISSN 1079-7440

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999)—Part I

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Overview

The chemical structure of a molecule determines the potential successful formulation approaches available to the parenteral scientist. However, there is no comprehensive listing of parenteral products with the chemical structure and formulation. A review of domestically marketed injectable product formulations of small molecule therapeutics is presented herein with the intent of compiling a comprehensive source of public information for the formulation scientist. The compilation lists the drug name, marketed name, chemical structure of the drug, marketed injectable formulation, preadministration preparation, route of administration, company and the clinical indication (1–7).

One purpose of this compilation is to assist the formulation scientist in being able to look at a drug's chemical structure and then be able to determine possible formulation approaches. This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

There are a few published reviews on parenteral formulations (8) and in an excellent review article (9) Lilly scientists, Sweetana and Akers, discuss the various formulation approaches with detailed tables of examples. In a compendium of excipients for parenteral formulations (10) Genentech scientists, Powell, Nguyen and Baloian, list the acceptable excipients as well as their percent's within the formulations, route of administration and pH. The compilation herein is an additional resource to the parenteral scientist by presenting the chemical structure and the formulation in a side-by-side fashion. An examination of this compilation reveals many examples of injectable formulation techniques to improve solubility or provide a sustained release. The next few sections highlight various formulation approaches with specific examples and tables, as well as general discussions of parenteral formulations.

Editor's Note: This review article on Injectable Products is being published in several parts. The next installment(s) will appear in subsequent issues of the *Journal*.

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Introduction

The word "parenteral" is Latin for "other than intestine," thus by definition the parenteral sciences not only includes injectable products but also transdermal, pulmonary, nasal, ophthalmic, and buccal routes of administration. However, in practice, parenteral usually refers to injectable products. Recently we have seen the commercialization of previously academic pursuits such as controlled-release formulations using microspheres, liposomes and polymeric gels, longer *in vivo* circulating times using PEGylated liposomes (also known as stealth liposomes) and PEGylated proteins, and new excipients such as cyclodextrin derivatives used as complexing agents for increasing water solubility of poorly soluble drugs. We have also seen the commercialization of injection devices such as prefilled syringes, dual chamber syringes containing solid drug and a liquid for reconstitution, and will likely soon see needle-free injectors and pocket-size infusion pumps.

Injectable Formulations

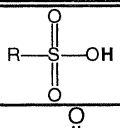
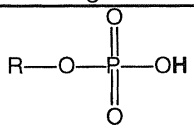
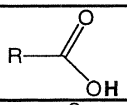
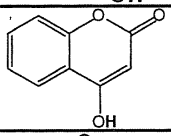
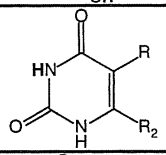
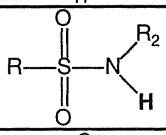
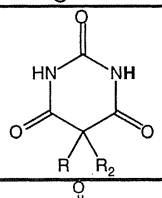
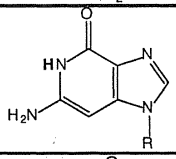
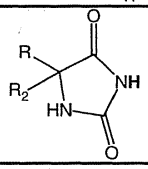
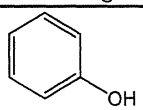
Two key aspects of any successful injectable formulation are: 1) to achieve the required drug concentration, and 2) the drug must be chemically and physically stable in order to have a sufficient shelf-life, which is generally considered to be the time for 10% degradation. The ideal injectable formulation, from an *in vivo* tolerability point-of-view, is isotonic with physiological fluids and a neutral pH (i.e., PBS: phosphate buffered saline, 0.01M sodium phosphate with 0.135M NaCl and 0.003M KCl, pH 7.4). However, in many instances the drug does not have sufficient water solubility at pH 7.4, and thus the formulation scientist must use a wide variety of solubilization techniques. If stability is insufficient to provide a two-year shelf-life, then the formulation scientist must either change the solution conditions to achieve both the solubility and stability requirements or develop a lyophilized product. This manuscript focuses on solubilization techniques for small molecules, and will not focus on stability or stabilization techniques.

I. Solubilization Techniques

1. pH Adjustment and Salts

If the drug molecule is ionizable, then pH adjustment can be utilized to increase water solubility since the ionized molecular species has higher water solubility than its neutral species. Indeed, the most common solubilization technique is pH adjustment and weak acids are normally formulated at

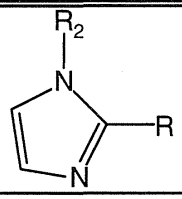
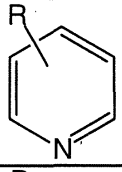
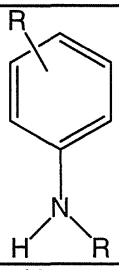
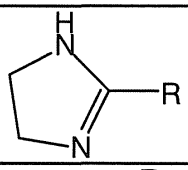
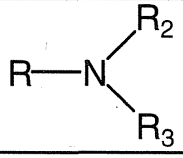
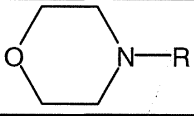
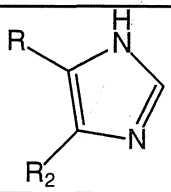
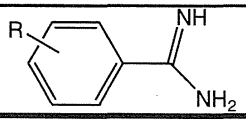
Table I. Examples of Weak Acid Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
Sulfonic acid		<1	Neutral	Aztreonam
Phosphate ester		2	Neutral	Fosphenytoin Bethamethasone Dexamethasone Fludarapine
Carboxylic acid		2.5-5	5-8	Penicillin Ketorolac
4-Hydroxy coumarin		~ 8	8.3	Warfarin
Uracil		~ 8	9.2	Flurouracil
Sulfonamide		7-9	9-11.6	Acetazolamide Clorothiazide Diazoxide
Barbituric acid		7-9	9.5-11	Methohexital Pentobarbital Phenobarbital Secobarbital
Guanine		2.2, 9.4	11	Acyclovir Gancyclovir
Hydantoin		~ 10	10-12	Phenytoin
Phenol		8-10	10.5 emulsion organic organic	Liothyronine Propofil Etoposide Teniposide

pH > 5 (Table I), weak bases at pH < 7 (Table II). Zwitterionic molecules have multiple ionizable groups and can be either cationic, anionic or neutral (positive and negative charges cancel each other, for an overall net neutral molecule) and are usually formulated at a pH in which the drug is ionic (Table III). For example, both ciprofloxacin and sufentanil have a carboxylic acid and an amine, but are formulated as the cation at pH < 7. On the other hand, both ampicillin and cephapirin have a carboxylic acid and an amine or pyridine, but are formulated as the anion at pH > 5.

The range in pH is quite broad and is between pH 2–12, and thus any molecule with a pKa between 3–11 can be potentially solubilized by pH adjustment. However, when using extremes in pH, care must be taken to minimize buffer capacity in order for the formulation to be *in vivo* compatible. When given intravenously, the formulation components are quickly diluted by the flow of blood and neutralized by the buffer capacity of blood. When given via intramuscular injection, the rate of dilution is reduced but rapid enough to still be able to inject in the range pH ~ 3–11. However

Table II. Examples of Weak Base Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
1H-Imidazole		~ 4-6	< 6	Miconazole Ondansetron
Pyridine		~ 5	2-4	Amronone Milrinone Papaverine Pyridoxine
Aniline		~ 5	2-6	Metoclopramide Minocycline (Procaine Procainamide also have a tertiary amine)
4,5-Imidazoline		~ 6	3-4	Tolazoline
Amine		7-10	3-7	Atenolol Codeine Daunorubicin Morphine Verapamil
N-Alky morpholine		7.4	< 5	Doxapram
Imidazole		~ 7	3-6.5	Cimetidine Dacarbazine Phentolamine
Amidine		~ 9-11	< 8	Pentamidine

when given subcutaneously the rate of dilution is reduced further with more potential for irritation at the injection site and thus the range is pH 3–6. For example, chlordiazepoxide is administered intravenously or intramuscularly and formulated at pH 3 with 20% propylene glycol and 4% TWEEN 20. Phenytoin sodium is administered either intravenously or intramuscularly and formulated at pH 10–12 with 40% propylene glycol and 10% ethanol. Subcutaneous formulations are slightly acidic such as methadone at pH 3–6, and levorphanol at pH 4.3.

Water-soluble salt forms (i.e., sodium salts of weak acids, or hydrochloride salts of weak bases) utilize the same principle of ionization, and are often the marketed form of the drug (Table IV). The most common cationic counterion is sodium which accounts for > 90% of the cations, and there are three meglumine salts, while only one salt each of

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